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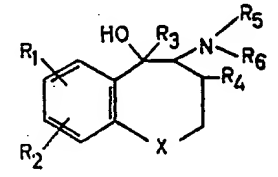
(54) AMINES

(71) We, BOEHRINGER INGELHEIM G.M.B.H. a German Body Corporate of Ingelheim am Rhein, Germany, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention is concerned with new amine derivatives having valuable pharmacological properties.

According to the present invention, we provide compounds of the general formula

I 

[wherein R_1 and R_2, which may be the same or different, each represents a hydrogen or halogen atom, a methyl or methoxy group or a trifluoromethyl, nitrile or hydroxy group, or, R_1 and R_2 together with the adjacent aromatic ring represent a naphthalene, indane, tetrahydronaphthalene, benz - 1,3 - dioxide or benzodioxane ring system;

R_3 represents a hydrogen atom, a methyl or ethyl group or a phenyl group which may be substituted in at least one position with a methyl group;

R_4 represents a hydrogen atom, a methyl or ethyl group, or a phenyl group which may be substituted with a halogen atom or a methyl or methoxy group;

R_5 represents a hydrogen atom, an alkyl group containing from 1 to 3 carbon atoms or a benzyl group which may be substituted with a halogen atom and/or an alkyl group containin gfrom 1 to 3 carbon atoms;

R_6 represents a hydrogen atom or an alkyl group containing from 1 to 3 carbon atoms, or, together with R_5 and the adjacent nitrogen atom, forms a pyrrolidino, piperidino or morpholino group, or a 5- or 6-membered heterocyclic ring containing a further nitrogen atom which may be substituted at the further nitrogen atom with a methyl or ethyl group or a phenyl group, which phenyl group may be substituted in at least one position by a halogen atom and/or a methyl and/or ethyl group; and

X represents an oxygen or sulphur atom or a methylene group; providing that when X represents an oxygen atom and R_1 and R_2 represent methyl groups in the 7- and 8-positions, at least one of the symbols R_3, R_4, R_5 and R_6 has a meaning other than hydrogen and when X represents a sulphur atom, at least one of the symbols R_1, R_2, R_3, R_4, R_5 and R_6 has a meaning other than hydrogen] and acid-addition salts thereof.

It will be appreciated that the compounds according to the invention contain at least two asymmetric centres, namely the 4- and

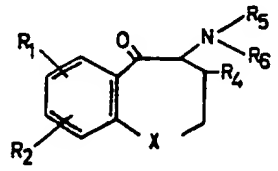
5-carbon atoms of formula I. They can thus exist in four stereoisomeric forms, as two pairs of optically active isomers. In one pair the hydr xyl group in 5-position and the amino group in 4-position are in the trans-position, and in the other pair they are in the cis-position. Both the racemic and the optically active isomers of the compounds of formula I are included within the scope of the present invention.

If R_3 has a meaning other than hydrogen, the compounds of formula I have a further centre of asymmetry and the number of stereoisomeric forms is then increased to 8.

The respective optically active isomers form racemates in usual manner.

The compounds according to the invention may be prepared according to any convenient process. However, the following process are particularly advantageous and constitute further features of the invention.

1) A process for the preparation of compounds of formula I (as hereinbefore defined) which comprises reacting a compound of formula

II 

(in which R_1, R_2, R_4, R_5, R_6 and X are as hereinbefore defined) with a reducing agent whereby the ketonic oxygen atom is converted into a hydroxyl group with simultaneous introduction of the group R_3 (as hereinbefore defined) at the 5-position.

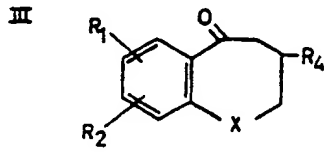
When it is desired to prepare compounds of formula I in which R_3 represents hydrogen, the reducing agent is conveniently catalytically activated hydrogen, hydrogen prepared from sodium in a lower alkanol, aluminoum isopropylate or a complex metal hydride such as lithium aluminium hydride or sodium borohydride. However, when it is desired to prepare compounds of formula I in which R_3 has a meaning other than hydrogen, the reducing agent is conveniently a methyl, ethyl or phenyl magnesium halide, if desired, the phenyl nucleus of the last-mentioned compound being substituted in at least one position by a methyl group.

According to the above-described process, the racemates of the cis- and the trans-form are obtained simultaneously. A separation of the two racemates may be effected by fractional crystallisation or by chromatography on silica gel. The compounds in which one of the symbols R_5 and R_6 represents a hydrogen atom namely secondary amino compounds, can also be separated by treating the mixture of isomers with aldehydes or ketones, preferably benzaldehyde or *p*-nitrobenzaldehyde, since the trans-compounds of formula I react with these compounds to form oxazolidines, whilst the cis-compounds are inert to aldehydes and ketones. Owing to its markedly changed solubility, the oxazolidine formed can be readily separated from the unchanged cis-compound and then again resolved into the starting components by treatment with dilute mineral acid.

The racemates of the cis- and trans- form can be resolved into their optically active isomers according to conventional processes, for example by salt formation with optically active auxiliary acids, such as dibenzoyl - D - tartaric acid or (+)3 - bromocamphor - 8 - sulphonic acid, subsequent fractional crystallisation of the diastereomeric salts and liberation of the bases.

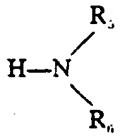
The above-described methods of separation can be applied in analogous manner to the compounds obtained according to the other processes.

The starting materials of the general formula II may for example be obtained from compounds of formula

III 

(in which R_1, R_2, R_4 and X are as hereinbefore defined) by three different routes.

Firstly, the appropriate compound of formula III may be brominated in the 4-position, with subsequent exchange of the bromine atom by reaction with the amine of formula



(in which R_5 and R_6 are as hereinbefore defined).

Secondly the 5-keto group of a compound of the general formula III may be oximated (analogously to the method described in Example 1 of U.S. Patent No. 3,243,439) with the aid of hydroxylamine, the oxime obtained reacted with toluene sulphonyl chloride (according to Example II of the above-mentioned U.S. Patent) and the resulting O - *p* - tosyl - oxime converted into the corresponding free amino compound of the general formula II (analogously to Example III of the US Patent).

Thirdly, compounds of the general formula II may be prepared from compounds of the

general formula III according to the method described by O. Dunn and W. D. Arndt in Liebigs Annalen 587 p. 50 (1954) namely the introduction with the aid of an organic nitrile of an oximino group at the 4-position of the starting material of formula III and the conversion of the compound obtained by means of catalytic hydrogenation into the corresponding compound of formula II containing a primary amino group at the 4-position.

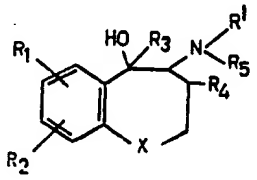
2) A process for the preparation of compounds of formula I (in which R_1, R_2, R_3, R_4 and X are as hereinbefore defined, R_5 represents a hydrogen atom and R_6 represents an alkyl group containing 1 to 3 carbon atoms or a benzyl group which may be substituted by a halogen atom and/or an alkyl group containing from 1 to 3 carbon atoms) which comprises reacting a compound of formula I (in which R_1, R_2, R_3, R_4 and X are as hereinbefore defined, and R_5 and R_6 both represent hydrogen atoms) with an appropriate alkylating of benzylating agent whereby the group represented by R_6 is introduced at the amino nitrogen atom.

It should be noted that the starting materials of formula I for the above-described process may include those compounds excluded by the proviso to the definition of formula I.

The alkylating agent may be a conventional alkylating agent, e.g. an alkyl halide, alkyl sulphonate or acetone and catalytically activated hydrogen, while the benzylating agent may be a conventional benzylating agent.

3) A process for the preparation of compounds of general formula I (in which R_1, R_2, R_3, R_4, R_5 and X are as hereinbefore defined and R_6 represents a hydrogen atom) which comprises hydrolysing or hydrogenolysing a compound of formula

IV



(in which R_1, R_2, R_3, R_4, R_5 and X are as hereinbefore defined and R′ represents a protecting group, removable by hydrolysis or hydrogenolysis, providing that when R_5 represents a benzyl group, R′ represents a protecting group removable by hydrolysis) whereby said protecting group is removed.

The protecting group may for example be an acyl or benzyl group.

4) A process for the preparation of compounds of formula I (in which R_1, R_2, R_3, R_4 and X are as hereinbefore defined and R_5 and R_6 have a meaning other than hydrogen) which comprises reacting a compound of formula I (in which R_1, R_2, R_3, R_4 and X are as hereinbefore defined and R_5 and R_6 represent hydrogen) with an appropriate alkylating or benzylating agent.

For the preparation of compounds of formula I (in which R_5 and R_6 represent the same alkyl group) from corresponding compounds of formula I (in which R_5 and R_6 represent hydrogen atoms) the introduction of the two alkyl groups is preferably effected in a single step. Thus, the alkylation according to process 2) is continued after the monoalkylation stage is complete until dialkylation is effected; alkyl halides or alkyl esters of sulphonic acids are preferred in this case as alkylating agents.

The compounds of formula I according to the invention obtained according to processes 2) to 4) may, if desired, be resolved in the manner described in process 1) into the individual racemates or individual optical isomers.

The above-described alkylation and resolution procedures may be carried out using compounds in either the cis- or trans- series; racemic or optically active starting materials may be used in these reactions.

Due to the presence of an amino group in the molecule, the compounds of formula I are bases and may therefore be converted into acid addition salts by treatment with the appropriate acid.

The acid adidtion salts may generally be used in the purification of the free bases. However, when the salts are to be used as medicines they must be non-toxic acid addition salts.

By the term "non-toxic acid addition salts" we mean those salts, the anionic moieties of which are physiologically compatible in the dosages at which the salts are administered.

Preferred acids for the preparation of non-toxic acid addition salts include hydrochloric acid, hydrobromic acid, sulphuric acid, succinic acid, maleic acid, tartaric acid, lactic acid, methanesulphonic acid, or acidic resins of the cross-linked polystyrene type containing sulphonic acid groups, such as Zeo-Karb 225 (the word "Zeo-Karb" is a Registered Trade Mark).

The compounds of the general formula I have interesting pharmacological properties, in particular antidepressive and anticonvulsive actions, accompanied by low toxicity. Particularly valuable compounds according to the invention are those compounds of the cis- or trans- series which are compounds of formula I in which at least one of the symbols R_1, R_2 and R_3 represents an alkyl group preferably wherein R_3 represents a methyl group and R_4 and R_5 represent hydrogen atoms, whilst R_4 and X have the above-given meanings, or, alternatively one of the symbols R_1, R_2 and R_3 represents a methyl group although

advantageously one of the groups R_1 and R_2 is a methyl group and the remaining group has a meaning other than a methyl group.

The following compounds according to the invention and their non-toxic acid addition salts are especially preferred by virtue of their favourable pharmacological activity:

racemic and optically active cis - 4 - methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine;

racemic and optically active trans - 4 - methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine;

racemic and optically active cis - 4 - methylamino - 5 - hydroxy - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine;

racemic and optically active trans - 4 - methylamino - 5 - hydroxy - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine;

racemic and optically active cis - 4 - dimethylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine;

racemic and optically active trans - 4 - dimethylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine;

racemic and optically active cis - 4 - methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydrobenzocycloheptene;

racemic and optically active trans - 4 - methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydrobenzocycloheptene;

racemic and optically active cis - 4 - methylamino - 3,7,8 - trimethyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine;

racemic and optically active trans - 4 - methylamino - 3,7,8 - trimethyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine;

racemic and optically active cis - 4 - methylamino - 8 - methyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine;

racemic and optically active trans - 4 - methylamino - 8 - methyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine;

racemic and optically active cis - 7 - chloro - 9 - methyl - 4 - methylamino - 5 - hydroxy - 2,3,4,5 - tetrahydrobenzoxepine; and

racemic and optically active trans - 7 - chloro - 9 - methyl - 4 - methylamino - 5 - hydroxy - 2,3,4,5 - tetrahydrobenzoxepine.

In particular, the optical isomers and the racemate of the trans-form of the 4-methyl amino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine hydrochloride, 4 - methylamino - 5 - hydroxy - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine hydrochloride, 4 - methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - benzocycloheptene and 4 - dimethylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine hydrochloride exhibit a particularly marked antidepressive activity, while the optical isomers and the racemate of the trans-form of 4 - methylamino - 3,7,8 - trimethyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine are valuable as anticonvulsive agents.

According to the present invention therefore we provide pharmaceutical compositions comprising, as active ingredient at least one compound of formula I (as hereinbefore defined) or a non-toxic acid addition salt thereof in association with a pharmaceutical carrier or excipient.

The pharmaceutical compositions according to the invention are preferably presented in the form of dosage units, each dosage unit being adapted to supply a fixed dose of active ingredient.

For oral administration of the trans-compounds of formula I each dosage unit preferably contains 1 to 250 mg of active ingredient, a convenient daily dose being 30 to 500 mg of active ingredient; for the three racemates and their optically active isomers indicated in the formula, for example, a single dose of 2 to 75 mg. and a daily dose of 30 to 150 mg. are particularly preferred.

The compounds according to the invention can be used alone, in combination with other active substances according to the invention and, if desired, in combination with further pharmacologically active ingredients, such as sympathicomimetics or psychopharmaceuticals. Advantageous forms of the pharmaceutical compositions according to the invention include, for example, tablets, capsules, suppositories, solutions, syrups, emulsions or dispersible powders. Tablets may be prepared, for example, by mixing the active substance(s) with convenient excipients, for example inert diluents, such as calcium carbonate, calcium phosphate or lactose, disintegrating agents, such as maize starch or alginic acid, binding agents, such as starch or gelatine, lubricants, such as magnesium stearate or talc, and/or agents for achieving a depot effect, such as carboxypolymethylene, carboxymethyl cellulose, cellulose acetate-phthalate or polyvinyl acetate.

The tablets may, if desired, be coated with several layers. Similarly dragees can be prepared by coating cores, prepared in an analogous manner to the tablets, with agents conventionally used in the preparation of dragee coatings, e.g. collidon or shellac, gum

arabic, talc, titanium dioxide or sugar. In order to achieve a depot effect or to avoid the contact of incompatible compounds, the core can also consist of several layers. In order to achieve a depot effect, the degree coat can likewise consist of several layers, wherein the above-mentioned excipients can be used.

Syrups containing the active ingredient according to the invention may additionally contain a sweetening agent, such as saccharin, cyclamate, glycerol or sugar, as well as a taste-improving agent, e.g. flavouring agents, such as vanillin or orange extract. Moreover they may further contain suspending excipients or thickeners, such as sodium carboxymethyl cellulose, wetting agents, for example condensation products of fatty alcohols and ethyleneoxide, or preservatives, such as *p*-hydroxybenzoates.

Injection solutions may be prepared in conventional manner e.g. with the addition of preservatives, such as *p*-hydroxybenzoates, or stabilisers, such as the alkali metal salts of ethylenediamine-tetraacetic acid, and filled into injection flasks or ampoules.

The capsules containing the active ingredient may be prepared, for example, by mixing the active ingredient with inert carriers, such as lactose or sorbitol, and encapsulating in gelatine capsules.

Suppositories may be prepared, for example, by mixing the active ingredient with conventional carrier substances, such as neutral fats or polyethylene glycol or its derivatives.

The following examples illustrate the invention.

Example 1

4 - N - Benzyl - N - methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

15 g. of sodium borohydride are added with stirring but without cooling over 10—15 minutes to 0.2 mol (61.8 g.) of racemic 4 - N - benzyl - N - methylamino - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one (m.p. 85—87°C), dissolved in 1 litre of methanol. The reaction mixture gradually warms up with foaming, and is then boiled under reflux for one further hour, evaporated in vacuo, the residue diluted with water and extracted with methylene chloride. After evaporating off the solvent, 60—62 g. of the crystalline isomer mixture remain. The racemic trans-component can be obtained by repeated crystallisations from methanol. It is, however, advantageous to subject the mixture to chromatographic adsorption on a volumn of 400—500 g. of thermally activated silica gel using a mixture of isopropyl ether/diethylamine (50:1) as eluting agent. 25—30 g. of racemic trans - 4 - N - benzyl - N - methyl - amino - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 5 - hydroxy - 1 - benzoxepine of m.p. 111—112°C, and upon further elution, 10—15 g. of the corresponding racemate of the cis-compound of m.p. 94—95°C are obtained.

The starting material is obtained as follows:

3,4 - Dimethylphenol is converted into 3,4 - dimethylphenoxy - butyric acid either according to the method of O. Dann and W. D. Arndt [Liebigs Annalen 587, p. 50] or, more preferably, by reaction of the sodium salt with butyrolactone according to B. Dotzauer [Thesis Marburg (1959), p. 55] and cyclised with polyphosphoric acid.

0.5 mol (95 g.) of 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 3 - one in 500 c.c. of chloroform are brominated with 80 g. of bromine. The reaction which starts immediately is completed after 15 minutes. The product is evaporated to dryness in vacuo and the solid residue is refluxed with 121 g. of N - benzyl - methylamine and 400 c.c. of xylene or toluene for 30 minutes; the N - benzyl - N - methylamine hydrobromide is shaken with water and the reaction product extracted with 2N hydrochloric acid.

The hydrochloric acid extracts are made alkaline extracted with methylene chloride and recrystallised from methanol to yield 78—85 g. (50—55% of theory) of racemic 4 - N - benzyl - N - methylamino - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one, m.p.: 85—87°C.

Example 2

4 - Methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

30 g. of the racemic trans-benzyl compound prepared according to Example 1, are hydrogenated in 200—250 c.c. of glacial acetic acid using palladium charcoal, the reaction product is filtered and the filtrate evaporated, the residue being dissolved in water and ammonia added to precipitate 70—80% of theory of the product in the form of colourless crystals of m.p. 117—118°C.

The colourless hydrochloride of the racemic trans-title compound of m.p. 210°C are obtained by treatment of the base with hydrochloric acid in an ethanol/ether mixture.

The cis-isomer is hydrogenated in analogous manner and the resulting racemic cis-base of the title compound, m.p. 150—151°C converted into the hydrochloride, m.p. 175—176°C.

Example 3

4 - Methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The mixture of the isomeric racemates of 4 - N - benzyl - N - methyl - amino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine (60—62 g). remain-

ing after the borohydride reaction according to Example 1 is directly hydrogenated in glacial acetic acid and the reaction product precipitated with ammonia (30—35 g.). The mixture of the cis- and trans-racemate of the title compound is boiled for 2 hours in a water separator with 30 g. of nitrobenzaldehyde in 400 c.c. of xylene. The product is evaporated in vacuo and placed on a short silica gel column (eluting agent: isopropyl ether). 15—20 g. of the corresponding oxazolidine of m.p. 101—102°C are obtained as first fraction. The oxazolidine is heated for 15 minutes with N hydrochloric acid on a water bath. The desired racemic trans-component of the base of m.p. 114—116°C is obtained by treatment of the filtrate with ammonia.

EXAMPLE 4

4 - Isopropylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

A suspension of 0.1 mol (31.4 g.) of racemic 4 - isopropyl - amino - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one hydrochloride (m.p. 225—227°C) in 1 litre of isopropanol is added to a mixture of 16.6 g. of sodium borohydride and 1 litre of isopropanol and the mixture stirred for 48 hours at room temperature. After the addition of 100 c.c. of water, the reaction mixture is stirred for a further hour and then filtered with suction. The filtrate is evaporated in vacuo and the residue subjected to chromatographic adsorption as in Example 1. Yield: racemic trans-base 5—7 g. m.p. 115—117°C racemic cis-base 3—4 g. m.p. 141—142°C.

Preparation of the starting material:

0.5 mol (95 g.) of 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one is brominated in a manner analogous to that described in Example 1 and the residue stirred in 500 c.c. of benzene with 120 g. of isopropylamine (100%) for 75 hours at room temperature. After the addition of 2N-hydrochloric acid, the sparingly soluble 4 - isopropylamino - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one hydrochloride precipitates out. Yield: 75—80 g.; m.p. 225—227°C.

EXAMPLE 5

4 - Diethylamino - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzothiepine

0.1 Mol (22.2 g.) of 4 - diethylamino - 2,3,4,5 - tetrahydro - 1 - benzothiepin - 5 - one (obtained by bromination of 2,3,4,5 - tetrahydro - 1 - benzothiepin - 5 - one—m.p. of the 4-bromo compound: 85—87°C—and subsequent amination of the bromo compound with a 10% diethylamine solution for 20 hours at 55—60°C) in 250 c.c. of methanol are reduced according to the method of Example 1 with 7.5 g. of sodium borohydride. After working up and chromatographic separation, the racemic trans-base of m.p. 146—148°C and the racemic cis-base of m.p. 86—87°C are obtained.

EXAMPLE 6

4 - Dimethylamino - 5 - hydroxy - 5,7, 8 - trimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

5.0. g. of 4 - dimethylamino - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one (obtained from the corresponding 4-bromo compound by treatment with a solution of dimethylamine in benzene) in 25 c.c. of ether are added to a Grignard solution of 1.8 g. of magnesium, 10 g. of methyl iodide and 25 c.c. of ether; the reaction mixture is boiled for 30 minutes, cold ammonium chloride solution is added, the solvent separated off and the residue of the ethereal solution subjected to chromatographic adsorption as described in Example 1. Yield: 20% of theory of the racemic trans-base of m.p. 88—90°C.

EXAMPLE 7

4 - Methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydrobenzocycloheptene

0.2 Mol of 7,8 - dimethyl - benzosuberan - 5 - one of b.p.$_{0.1}$ 102—104°C (prepared by reaction of *o*-xylene with glutaric acid anhydride/aluminium chloride, reduction of the resulting keto compound and subsequent cyclisation with polyphosphoric acid) were brominated analogously to Example 1 and aminated with N-benzylmethylamine. Reduction with sodium borohydride, chromatographic separation and reductive debenzylation yielded the racemic trans-base of the title compound of m.p. 149—150°C. (hydrochloride: m.p. 212—213°C).

EXAMPLE 8

8 - Chloro - 4 - methylamino - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

11 g of racemic trans - 8 - chloro - 4 - benzylmethylamino - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine hydrochloride (prepared analogously to Example 1) are hydrogenated in 100 c.c. of water and 50 c.c. of methanol after the addition of 1.5 g. of charcoal and 15 c.c. of 2% palladium chloride at 60°C and under 5 atmospheres pressure. After 3 to 5 minutes, 90% of the hydrogen necessary for splitting off the benzyl group is taken up and the rate of hydrogenation becomes much slower. Hydrogenation is discontinued and the product worked up analogously to Example 1.

Yield: 75% of colourless crystals from isopropyl ether; m.p. 121—122°C (transbase).

EXAMPLE 9

4 - Diethylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

0.5 Mol (95 g.) of 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one are brominated analogously to Example 1 and aminated with 500 c.c. of a 10% solution of dimethylamine in benzene over 1 hour at room temperature and then over 2 hours at 50°C; the subsequent reduction and separation are effected analogously to Example 1.

The racemic trans-base of m.p. 103—104°C (hydrochloric: m.p. 131—132°C) and the racemic cis-base of m.p. 141—142°C (hydrochloride: m.p. 215—217°C) are obtained.

EXAMPLE 10

4 - Morpholino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The preparation is effected in a manner analogous to that described in Example 1, starting from 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one, which is brominated and the bromo-compound reacted with morpholine. The reaction product is reduced with sodium borohydride and separated by chromatography.

The racemic trans-base, m.p. 135—136°C and racemic cis-base, m.p. 145—146°C are thereby obtained.

EXAMPLE 11

4 - Piperidino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The preparation is effected in a manner analogous to that described in Example 1, starting from 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one which is brominated, the bromo-compound reacted with piperidine, the product reduced with sodium borohydride and the title compound separated by chromatography.

The racemic trans-base: m.p. 82—84°C and racemic cis-base: m.p. 175°C are thereby obtained.

EXAMPLE 12

4 - N - Phenylpiperazino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The preparation is effected in a manner analogous to that described in Example 1 starting from 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one which is brominated, and the bromo-compound reacted with N-phenylpiperazine, the resulting product reduced with sodium borohydride and the title compound separated by chromatography to yield the racemic cis-base, m.p. 205—207°C (hydrochloride: m.p. 231—233°C).

EXAMPLE 13

4 - N - Benzyl - N - methylamino - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The preparation is effected in a manner analogous to that described in Example 1, by converting phenol into phenoxybutyric acid which is cyclised with polyphosphoric acid, brominating the 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one obtained, then reacting the bromo-compound with N - benzyl - methylamine, reducing the product with sodium borohydride and separation of the title compound by chromatography to yield the racemic trans-base of m.p. 84—85°C and racemic cis-base of m.p. 107—108°C.

EXAMPLE 14

4 - Methylamino - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The preparation is effected in an analogous manner to that described in Example 2, starting from the corresponding end products of Example 13.

The racemic trans-base of m.p. 99—100°C (hydrochloride: m.p. 196—197°C), and the racemic cis-base of m.p. 125—126°C (hydrochloride: m.p. 150—152°C) are thereby obtained.

EXAMPLE 15

4 - N - Benzyl - N - methylamino - 5 - hydroxy - 8 - methoxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

Starting from resorcinol methyl ether, the preparation is effected in a manner analogous to that described in Example 1, the 3 - methoxy - phenoxybutyric acid being cyclised with polyphosphoric acid to give 8 - methoxy - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one which is brominated in the 4-position, followed by reaction with N - benzyl - methylamine, reduction with sodium borohydride and chromatographic separation to yield the racemic trans-base m.p. 105—107°C and the racemic cis-base m.p. 82—84°C.

EXAMPLE 16

4 - Methylamino - 5 - hydroxy - 8 - methoxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The preparation is effected in an analogous manner to that described in Example 2, starting from the corresponding end products of Example 15.

The racemic trans-base of m.p. 102—103°C (hydrochloride: m.p. 200—202°C) and the racemic cis-base of m.p. 125—126°C (hydrochloride: m.p. about 150°C) are thereby obtained.

EXAMPLE 17

4 - N - Benzyl - N - methylamino - 5 - hydroxy - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The preparation is effected as described in Example 1, starting from 2,4-xylenol which is converted into the 2,4 - dimethylphenoxybutyric acid. This is cyclised with polyphosphoric acid to yield the 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one of b.p.$_{0.2}$ 116—118°C which is brominated, then reacted with N - benzyl - methylamine reduced with sodium borohydride and separated chromatographically to yield the racemic trans-base: m.p. 105—107°C, and the racemic cis-base: m.p. 89—91°C.

Example 18

4 - Methylamino - 5 - hydroxy - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The preparation takes place as described in Example 2, starting from the benzyl derivatives of Example 17. There are thus obtained: racemic trans-base of m.p. 112—113°C, (hydrochloride: 185—186°C) and the racemic cis-base of m.p. 114—115°C (hydrochloride: m.p. 215—216°C).

Example 19

4 - Dimethylamino - 5 - hydroxy - 8 - chloro - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The preparation takes place as described in Example 1, starting from 3-chlorophenol via 3-chlorophenoxybutyric acid and 8 - chloro - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one.

The latter is brominated, reacted with a dimethyl amine solution, reduced with sodium borohydride and separated chromatographically to yield the racemic trans-base: m.p. 61—63°C and the racemic cis-base: m.p. 134—135°C.

Example 20

4 - Dimethylamino - 5 - hydroxy - 7 - chloro - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The preparation takes place as indicated in Example 1, starting from 4 - chlorophenol via 4 - chlorophenoxybutyric acid and 8 - chloro - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one. The latter is brominated, reacted with dimethylamine and separated chromatographically to yield the racemic trans-base of m.p. 119—120°C, and racemic cis-base of m.p. 118—120°C.

Example 21

4 - Dimethylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - benzocycloheptene

The preparation is effected in a manner analogous to that described in Example 7, via 7,8 - dimethyl - benzosuberan - 5 - one and the corresponding 4-bromo compound which is reacted with dimethylamine, reduced with sodium borohydride and separated chromatographically to yield the racemic trans-base of m.p. 76—77°C.

Example 22

4 - N - Benzyl - N - methylamino - 3,7,8 - trimethyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

Starting from 3,4 - dimethyl phenol and ethyl bromo - β - methyl - crotonate 3,7,8 - trimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one of b.p.$_{0.7}$ 110—112°C is prepared according to Example 1. The product is brominated, reacted with N - benzyl - methylamine and reduced with sodium borohydride to yield, after separation by column chromatography, the oily cis- and trans-compounds.

Example 23

Trans - 4 - methylamino - 3,7,8 - trimethyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The trans-compound obtained according to Example 22 is debenzylated according to Example 2. M.p. of the title compound 111—113°C.

Example 24

4 - N - Benzyl - N - methylamino - 8 - methyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

Starting from *o*-cresol and butyrolactone, the title compound is obtained as described in Example 1.

Trans-compound, m.p. 58—60°C. Cis-compound m.p. 99—100°C.

Example 25

4 - Methylamino - 8 - methyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The title compound is obtained by debenzylation according to Example 2 of the compounds prepared according to Example 24. Trans-base m.p. 81—82°C (hydrochloride m.p. 231—232°C). Cis-base m.p. 146—148°C (hydrochloride m.p. 182—183°C).

Example 26

4 - N - Benzyl - N - methylamino - 7 - chloro - 9 - methyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

The title compound is obtained in a manner analogous to that described in Example 1 by starting from 2 - methyl - 4 - chlorophenol and butyrolactone. Trans-base m.p. 140—141°C. Cis-base m.p. 91—92°C.

Example 27

Trans - 4 - methylamino - 7 - chloro - 9 - methyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

Mild catalytic debenzylation in water/

methanol according to Example 8 of the trans-base obtained according to Example 26 yields the title compound; m.p. 141—142°C.

Example 28

Trans - 4 - amino - 7,9 - dimethyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

38.0 g. of 4 - amino - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one hydrochloride are hydrogenated with 15 g. of Raney nickel in 500 ml. of water under 5 atmospheres pressure and at 60°C. After filtering off the catalyst with suction, the base is liberated with ammonia and extracted with a large amount of ether. The dried ethereal solution is evaporated to about 300 ml., whereby the desired transform crystallises out. After recrystallising from isopropyl ether, 5—8 g. of the title compound of m.p. 138—140° are obtained. The hydrochloride prepared therefrom melts at 245—248°C.

The starting material was obtained as follows:

19 g. of 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one (see Example 17) are oximated according to O. Dann and W. D. Arndt, [Liebigs Annalen 587, p. 50 (1954)] to give 18.4 g. of the oximino compound of m.p. 153—154. By hydrogenation with palladium in methanol/HCl. 9 g. of 4 - amino - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one hydrochloride of m.p. 210—211° are obtained therefrom.

Example 29

Trans - 4 - methylamino - 5 - hydroxy - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine

30 g. of 4 - methylamino - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one hydrochloride in 300 ml. of water are hydrogenated with 10 g. of Raney nickel at 5 atmospheres and at 60°C. After filtering off the catalyst with suction, the base is liberated with ammonia and extracted with methylene chloride. The methylene chloride solution is evaporated and the residue recrystallised twice from isopropyl ether. 15 g. of the title compound of m.p. 112—115° are obtained.

The starting material was obtained as follows:

80 g. of 2,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one (see Example 17) are brominated and the bromo compound reacted with N - benzyl - methylamine, whereby 88 g. of 4 - N - benzyl - N - methylamino - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one of m.p. 78—79° are obtained.

The ketone is hydrogenated in 600 ml. of water, 150 ml. of 2N HCl and 350 ml. of methanol in the presence of 2 g. of charcoal and 50 ml. of a 2% palladium chloride solution at 60°C and under a pressure of 5 atmospheres. After filtering off the catalyst with suction, with solution is evaporated and the residue recrystallised from methanol. The 4 - methyl - amino - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepin - 5 - one hydrochloride is obtained in a yield of 75 g. m.p. 223—225°.

Example 30

Trans - 4 - Methylamino - 9 - methyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine

If the trans-base of Example 26 is hydrogenated in methanol whereby 2 mol of hydrogen are taken up, the dehalogenated title compound may be obtained (m.p. 79—80°C).

The title compound may likewise be obtained by reductive dehalogenation of the trans-base of Example 27.

Example 31

Trans - 4 - methylamino - 5 - hydroxy - 8,9 - dimethyl - 2,3,4,5 - tetrahydro - benzoxepine

The oily benzyl compound is obtained analogously to Example 1 from 2,3 - dimethylphenol and butyrolactone. Catalytic-reductive debenzylation in glacial acetic acid or methanol analogously to Example 8 yields the title compound. Trans-base m.p. 103—104° (hydrochloride: m.p. 218—219°).

The compounds obtained according to the above examples have been shown to be sterically uniform in the NMR-spectroscopic examination.

Examples of pharmaceutical compositions

A. Dragees

Composition

1 Dragee core contains:

4 - Methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine hydrochloride	15.0 mg
lactose	23.5 mg
Maize starch	10.0 mg
Gelatine	1.0 mg
Magnesium stearate	0.5 mg
	50.0 mg

Preparation:

The mixture of active substance with lactose and maize starch is granulated with a 10% aqueous gelatine solution through a sieve of a mesh width of 1 mm, dried at 40°C and then again ground through a sieve. The granulate thus obtained is mixed with magnesium stearate and pressed into cores. The cores thus obtained are coated in conventional manner with a coating which is applied by means of an aqueous suspension of sugar, titanium dioxide, talc and gum arabic. The finished

dragees are polished with the aid of beeswax. Final weight of the dragees: 100 mg.

B. Drops.
Composition:
100 ml of drop solution contains:

Methyl p - hydroxybenzoate	0.035	g
Propy p - hydroxybenzoate	0.015	g
Aniseed oil	0.05	g
Methanol	0.06	g
Ethanol, pure	10.00	g
4 - Methylamino - 5 - hydroxy-7,9 - dimethyl - 2,3,4,5 - tetra-hydro - 1 - benzoxepine hemi-succinate	1.00	g
Citric acid	0.7	g
Sodium phosphate sec. $2H_2O$	0.3	g
Sodium cyclamate	1.0	g
Glycerol	15.0	g
Bidist. water ad	100.0	ml

Preparation:
The p - hydroxybenzoates, aniseed oil and methanol are dissolved in ethanol (solution A) The buffer substances, active ingredient and sodium cyclamate are dissolved in distilled water and the glycerol is added (solution B).
Solution A is stirred into solution B and the mixture made up with bidistilled water to the desired volume. The final solution is filtered through a suitable filter.

C. Suppositories:
1 Suppository contains:

4 - Dimethylamino - 5 - hydroxy-7,8 - dimethyl - 2,3,4,5 - tetra-hydro - 1 - benzoxepine - methanesulphonate	25 mg
Suppository base (e.g. Witepsol W 45; the word "Witepsol" is a registered Trade Mark; a mixture of triglycerides)	1675 mg

Preparation:
The finely powdered active ingredient is stirred into the suppository base which is melted and cooled to 40°C, by means of an immersion homogeniser. The base is poured into slightly pre-cooled moulds at 35°C.

D. Ampoule:
1 Ampoule contains

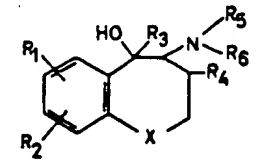
4 - methylamine - 5 - hydroxy-7,8 - dimethyl - 2,3,4 - tetra-hydro - 1 - benzocycloheptene	20.0 mg
Citric acid	7.0 mg
Sodium phosphate sec. $2H_2O$	3.0 mg
Sodium pyrosulphite	1.0 mg
Bidist. water ad	1.0 ml

Preparation:
The buffer substances, active substance and sodium pyrosulphite are successively dissolved in boiled water. The solution is made up to the given volume with boiled water and filtered pyrogen-free.

Sterilisation: 20 minutes at 120°C.

WHAT WE CLAIM IS:—

1. Compounds of the general formula

I 

[wherein R_1 and R_2, which may be the same or different, each represents a hydrogen or halogen atom, a methyl or methoxy group or a trifluoromethyl, nitrile or hydroxy group, or, R_1 and R_2 together with the adjacent aromatic ring represent a naphthalene, indane, tetrahydronaphthalene, benz - 1,3 - dioxide or benzodioxane ring system;

R_3 represents a hydrogen atom, a methyl or ethyl group or a phenyl group which may be substituted in at least one position with a methyl group;

R_4 represents a hydrogen atom, a methyl or ethyl group, or a phenyl group which may be substituted with a halogen atom or a methyl or methoxy group;

R_5 represents a hydrogen atom, an alkyl group containing from 1 to 3 carbon atoms or a benzyl group which may be substituted with a halogen atom and/or an alkyl group containing from 1 to 3 carbon atoms;

R_6 represents a hydrogen atom or an alkyl group containing from 1 to 3 carbon atoms, or, together with R_5 and the adjacent nitrogen atom, forms a pyrrolidino, piperidino, or morpholino group, or a 5- or 6- membered heterocyclic ring containing a further nitrogen atom which may be substituted at the further nitrogen atom with a methyl or ethyl group or a phenyl group, which phenyl group may be substituted in at least one position by a halogen atom and/or a methyl and/or ethyl group; and

X represents an oxygen or sulphur atom or a methylene group; providing that when X represents an oxygen atom and R_1 and R_2 represent methyl groups in the 7- and 8-positions, at least one of the symbols R_3, R_4, R_5 and R_6 has a meaning other than hydrogen and, when X represents a sulphur atom, at least one of the symbols R_1, R_2, R_3, R_4, R_5, and R_6 has a meaning other than hydrogen] and acid-addition salts thereof.

2. Racemic and optionally active cis- compounds of formula I (as defined in claim 1) and acid addition salts thereof.

3. Racemic and optionally active trans-compounds of formula I (as defined in claim 1) and acid addition salts thereof.

4. Compounds as claimed in any of the preceding claims in which at least one of the symbols R_1, R_2, and R_3 of formula I represents an alkyl group, R_3 and R_6 represent hydrogen atoms and R_4 and X are as defined in claim 1.

5. Compounds as claimed in claim 4 in which at least one of the symbols R_1, R_2 and R_3 represents a methyl group.

6. Racemic and optionally active cis - 4 - methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine and acid addition salts thereof.

7. Racemic and optically active trans - 4 - methylamino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine and acid addition salts thereof.

8. Racemic and optically active cis - 4 - methylamino - 5 - hydroxy - 7,9 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benzoxepine and acid addition salts thereof.

9. Racemic and optically active trans - 4 - methylamino - 5 - hydroxy - 7,9 - dimethyl- 2,3,4,5 - tetrahydro - 1 - benzoxepine and acid addition salts thereof.

10. Racemic and optically active cis - 4 - dimethylamino - 5 - hydroxy - 7,8 - dimethyl- 2,3,4,5 - tetrahydro - 1 - benzoxepine and acid addition salts thereof.

11. Racemic and optically active trans - 4 - dimethyl - amino - 5 - hydroxy - 7,8 - dimethyl - 2,3,4,5 - tetrahydro - 1 - benz - oxepine and acid addition salts thereof.

12. Racemic and optically active cis - 4 - methylamino - 5 - hydroxy - 7,8 - dimethyl- 2,3,4,5 - tetrahydrobenzocycloheptene and acid addition salts thereof.

13. Racemic and optically active trans - 4 - methylamino - 5 - hydroxy - 7,8 - di - methyl - 2,3,4,5 - tetrahydrobenzocyclo - heptene and acid addition salts thereof.

14. Racemic and optically active cis - 4 - methylamino - 3,7,8 - trimethyl - 5 - hydroxy- 2,3,4,5 - tetrahydro - 1 - benzoxepine and acid addition salts thereof.

15. Racemic and optically active trans - 4 - methylamino - 3,7,8 - trimethyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine and acid addition salts thereof.

16. Racemic and optically active cis - 4 - methylamino - 8 - methyl - 5 - hydroxy - 2,3,4,5 - tetrahydro - 1 - benzoxepine and acid addition salts thereof.

17. Racemic and optically active trans - 4 - methylamino - 8 - methyl - 5 - hydroxy- 2,3,4,5 - tetrahydro - 1 - benzoxepine and acid addition salts thereof.

18. Racemic and optically active cis - 7 - chloro - 9 - methyl - 4 - methylamino - 5 - hydroxy - 2,3,4,5 - tetrahydrobenzoxepine and acid addition salts thereof.

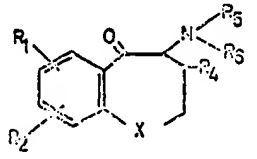
19. Racemic and optically active trans - 7 - chloro - 9 - methyl - 4 - methylamino - 5 - hydroxy - 2,3,4,5 - tetrahydrobenzoxepine and acid addition salts thereof.

20. Compounds as claimed in any of the preceding claims in the form of non-toxic acid addition salts thereof.

21. Compounds as claimed in claim 20 in the form of their acid addition salts with hydrochloric acid, hydrobromic acid, sulphuric acid, succinic acid, maleic acid, tartaric acid, lactic aid, methanesulphonic acid, or acidic resins of the cross-linked polystyrene type containing sulphonic acid groups.

22. A process for the preparation of compounds of formula I as defined in claim 1 which comprises reacting a compound of formula

II



(in which R_1, R_2, R_3, R_5, R_6 and X are as defined in claim 1) with a reducing agent whereby the ketonic oxygen atom is converted into a hydroxyl group with simultaneous introduction of the group R_5 (as defined in claim 1) at the 5-position.

23. A process as claimed in claim 22 for the preparation of compounds of formula I (in which R_5 represents hydrogen) in which the reducing agent is catalytically activated hydrogen, hydrogen prepared from sodium and a lower alkanol, aluminium iso - propylate or a complex metal hydride.

24. A process as claimed in claim 23 in which the complex metal hydride is lithium aluminium hydride or sodium borohydride.

25. A process as claimed in claim 22 for the preparation of compounds of formula I (in which R_5 has a meaning other than hydrogen) in which the reducing agent is a methyl, ethyl or phenyl magnesium halide.

26. A process as claimed in claim 25 in which the phenyl nucleus of the phenyl magnesium halide is substituted in at least one position by a methyl group.

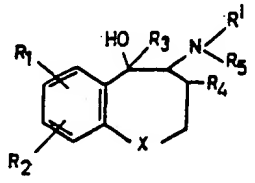
27. A process for the preparation of compounds of formula I (in which R_1, R_2, R_3, R_4 and X are as defined in claim 1, R_6 represents a hydrogen atom and R_5 represents an alkyl group containing from 1 to 3 carbon atoms or a benzyl group which may be substituted by a halogen atom and/or an alkyl group containing from 1 to 3 carbon atoms) which comprises reacting a compound of formula I (in which R_2, R_3, R_4, R_5, and X are as hereinbefore defined, and R_1 and R_6 both represent hydrogen atoms) with an

appropriate alkylating or benzylating agent whereby the group represented by R_5 is introduced at the amino nitrogen atom.

28. A process as claimed in claim 27 in which the alkylating agent is an alkyl halide or alkyl sulphonate, or acetone in the presence of catalytically activated hydrogen.

29. A process for the preparation of compounds of general formula I (in which R_1, R_2, R_3, R_4, R_5 and X are as defined in claim 1 and R_6 represents a hydrogen atom) which comprises hydrolysing or hydrogenolysing a compound of formula

IV



(in which R_1, R_2, R_3, R_4, R_5 and X are as defined in claim 1 and R′ represents a protecting group, removable by hydrolysis or hydrogenolysis, providing that when R_5 represents a benzyl group, R′ represents a protecting group removable by hydrolysis) whereby said protecting group is removed.

30. A process as claimed in claim 29 in which R′ represents an acyl group or a benzyl group.

31. A process for the preparation of compounds of formula I (in which R_1, R_2, R_3, R_4 and X are as defined in claim 1 and R_5 and R_6 have a meaning other than hydrogen) which comprises reacting a compound of formula I (in which R_1, R_2, R_3, R_4 and X are as defined in claim 1 and R_5 and R_6 represent hydrogen) with an appropriate alkylating or benzylating agent.

32. A process as claimed in claim 31 in which the alkylating agent is an alkyl halide or an alkyl ester of a sulphonic acid.

33. A process as claimed in any of claims 22 to 32 in which the racemates of the cis- and trans- forms of the compounds of formula I are subsequently separated.

34. A process as claimed in claim 33 in which the separation is effected by fractional crystallisation or chromatography.

35. A process as claimed in any of claims 22 to 34 in which the racemates of the cis and/or trans- forms of the compounds of formula I obtained are subsequently resolved into their optical isomers.

36. A process as claimed in any of claims 22 to 35 in which the compounds of formula I obtained are subsequently converted into an acid addition salt thereof by treatment with an appropriate acid.

37. A process as claimed in claim 36 in which the acid is hydrochloric acid, hydrobromic acid, sulphuric acid, succinic acid, maleic acid, tartaric acid, lactic acid, methanesulphonic acid, or an acidic resin of the cross-linked polystyrene type containing sulphonic acid groups.

38. A process as claimed in any of claims 22 to 37 substantially as herein described.

39. A process as claimed in any of claims 22 to 37 substantially as herein described in any of Examples 1 to 31.

40. Compounds of formula I (as defined in claim 1) and acid addition salts thereof whenever prepared by a process as claimed in any of claims 22 to 39.

41. Pharmaceutical compositions comprising, as active ingredient, at least one compound of formula I (as defined in claim 1) or a non-toxic acid addition salt thereof in association with a pharmaceutical carrier or excipient.

42. Pharmaceutical compositions as claimed in claim 41 in the form of dosage units.

43. Pharmaceutical compositions as claimed in claim 42 for oral administration in which each dosage unit contains 1 to 250 mg of active ingredient.

44. Pharmaceutical compositions as claimed in claim 43 in which each dosage unit contains 2 to 75 mg of active ingredient.

45. Pharmaceutical compositions as claimed in any of claims 42 to 44 in the form of dragees, suppositories or ampoules.

46. Pharmaceutical compositions as claimed in claim 41 in the form of drop solutions.

47. Pharmaceutical compositions as claimed in any of claims 41 to 46 including a further pharmacologically active ingredient.

48. Pharmaceutical compositions as claimed in claim 47 in which the further pharmacologically active ingredient is a sympathicomimetic or a psychopharmaceutical.

49. Pharmaceutical compositions as claimed in claim 41 substantially as herein described.

50. Pharmaceutical compositions as claimed in claim 41 substantially as herein described in any of Examples A to D.

For the Applicants.
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